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2005 SPEAKER SERIES:
DR. JOSEPH ROHAN LEX, JR., M.D. FAAEM
THE PHYSICIAN-PHARMACEUTICAL INDUSTRY
RELATIONSHIP

MR. MEARNS: Good afternoon, everyone. My name is Geoff Mearns and I'm the Dean of Cleveland Marshall College of Law and it's my pleasure to welcome you here to what I guess is chapter two of the inaugural lecture in the Journal of Law and Health lecture series.

If you had the pleasure of being here yesterday, you know that you are in for an informative and engaging presentation by Dr. Lex. And so without any further ado, I'm going to introduce Evelyn Holmer, she is co-editor-in-chief of the Journal of Law and Health and she will introduce Dr. Lex.

MS. HOLMER: Good evening. On behalf of the Cleveland Marshall Journal of Law and Health, I'd like to welcome you here this evening.

Before I get started, as a friendly reminder, if you haven't done so already, if you could just pull out your pagers, BlackBerries and cell phones, make sure you have them on vibrate or silent, I would greatly appreciate that.

All right. On to getting started.

Being one of only a handful of law reviews which encompass both the fields of law and health, the Journal seeks to serve Cleveland and its healthcare community by facilitating a link between the medical and legal professions. The Journal prides itself on constantly examining healthcare law from all angles, be it medicinal, constitutional or political. And in doing this, there are a variety of forums, be it from presenting speakers to publishing medical works to publishing law reviews. In fact, a transcript of tonight's presentation will be published in our next issue, numbered 18-2, which is due out in December, knock on wood.

Pursuant to this spirit, it is our honor to host Dr. Lex tonight. Dr. Lex is a graduate of the University of Texas Health Science Center and served his internship and residency at the Thomas Jefferson University Hospital in Philadelphia. He is a member of the Society for Academic Emergency Medicine, a member of the Physicians for National Health Plan, and also a Fellow of the American Academy for Emergency Medicine. He currently serves on the faculty at Temple University School of Medicine as an assistant professor of emergency medicine.

Dr. Lex's educational experience is outmatched only by his list of accolades, and this is where he's going to get embarrassed because we did this last night. Dr. Lex is the recipient of the Presidential Unit Citation of Valorous Action in Vietnam, the Combat Medical Badge for Service in Vietnam, the Temple University Excellence in Teaching Award, and the Vickery Award for Outstanding Contributions For Emergency Medicine Education, amongst many others.

Ladies and gentlemen, please join me in welcoming for the second time in our series Dr. Joseph Lex.

DR. LEX: Do I need to speak louder using the lavalier? Are you okay if I wander? Cool. Because I'm going to wander. All right.

Tonight's topic is actually four combined into one. If you thought last night's talk was truncated, two hours into one, tonight I'm going to cram four hours into one. So hang onto your hats.

I could actually divide this into four different talks. First of all, there's the ethics on giving gifts. Then there's the intertwining of academia and industry, which is pretty nasty, when you get right down to it. Then there's just the whole psychology of promotion. And finally, food, flattery and friendship. I hope to spend a little bit of time talking about some logical fallacies in pharmaceutical promotion. So I've got lots of things to get in here.

First of all, I've got to make confession. Once upon a time, I ate drug rep doughnuts and pizza. And I craved freebies at national meetings. I used to get my

little bag and go around, stuff the bag full of stuff. I attended drug company sponsored meals at one time in my career. I used to drink from a Monistat mug, I wrote with a Rocephin pen, I did all of these things. I even once, please forgive me, I went to a Phillies game on a drug company's dollar and I sat in their private box.

But that was a long time ago and I wish that I knew then what I know now. I have been clean for about fifteen years.

Now, I'm going to give you this: I have knowledge that pharmaceutical research and development is employing. Ten years ago age was a death sentence. Thirty years ago renal failure was a death sentence. Fifty years ago cancer was a death sentence. There have been remarkable strides in the pharmaceutical research, although much of the research actually comes from universities and is funded nationally rather than by the pharmaceutical industry. That's a whole different topic.

I will just acknowledge that some good comes out of the pharmaceutical industry. In addition, it is still happening. Not two days ago Bayer Pharmaceuticals announced that they were long moxifloxacin, one of their expensive new antibiotics, to be tested in the treatment of tuberculosis, and if it is found to be successful, they promised they will distributed it at cost in third world countries to try to eradicate tuberculosis. So drug companies are doing good things. And I'm not going to argue that.

My premise is that physician interactions with marketing representatives result in inevitable and irreconcilable conflicts of interest or the appearance of conflicts of interest. Our patients in medicine are the ultimate losers from such interactions.

So for recovery we have proposed these things, people who feel the way I do. We have to admit that we are powerless over pharmaceutical paraphernalia, that our lives have become unmanageable. We will make a searching and fearless moral inventory of ourselves, our desks and our work areas. We are entirely ready to remove all of these defects of character, as well as pens, penlights and notepads. And having have this spiritual awakening as a result of these steps, we try to carry the message to others, and to practice these principles in all of our affairs.

Does this sound familiar? What's TANSTAAFL? Who is a Heinlein fan? What does TANSTAAFL mean? There ain't no such thing as a free lunch. This is a quote. There ain't no such thing, and if there were, these drinks would cost half as much. Reminding us anything that is free costs twice as much in the long run or turns out worthless. This is from *The Moon is a Harsh Mistress*, 1966, Robert Heinlein.

But I hear you say or I hear my colleague physicians say nearly all organizations agree that it's okay to take small gifts from the drug companies. Or if, you know, if they don't market it to us as physicians, they are just going to turn around and market it directly to the consumer and the consumers aren't going to know how to handle that information. At least we can process and deal with that information. Or, you know, you are really an insulting boor to think that I can be bought so cheaply, that if I can be bought by a pen or a notepad, but you know something, I'm going to remind you that, as a lawyer and as a physician, we have a fiduciary relationship with our patients or with our clients. And what does this mean?

A fiduciary, we have a specialized knowledge or expertise, we hold the trust of others, we hold high standards of conduct, we avoid conflicts of interest, and we are accountable or obligated, both ethically and legally. This is the place where medicine and law have the same set of ethics.

I am a member of a profession. As a professional, society has asked that I serve its interests over my own interests. And in return, society trusts me to do what is right. This trust allows my profession to self-govern. Just as it allows your profession to self-govern.

The problem is, when we get into the promotional pharmaceutical, I'll get into that a little bit more, because most physicians are hard working, and most physicians desperately want to act in the patient's best interest, physicians do not like the image of being bought by drug companies. We like to see ourselves as independent thinkers, and this is not a very popular message among physicians. It's really not. Because most physicians think they are over all of this stuff that I am talking about.

But I want to show you something that I hope will make you understand where I'm coming from.

Companies are businesses, we live in a capitalist society, that's not going to change anytime soon, and pharmaceutical companies are not evil empires, for the most part. They are businesses. They are businesses. They are the most profitable business in the world, by far. They make huge amounts of money, and I'll show you statistics in a little while. They spend far more on marketing than they do on research and development, despite what they want to tell you. A majority -- or more money goes into marketing than it does into research and development, and the reason they spend the money on marketing is simple. It works.

In fact, as a business, it is their obligation to make as much money as possible for their stockholders. If the money they put into marketing did not work, it would be unethical for them to spend it on marketing because it was not returning a profit. So this is their ethics and this is what we have to look at. It's a different set of ethics from the fiduciary relationship that we have with our patients or our clients. Their business is the business of business. It's to make money.

Drug companies do not advertise to capture our forebrains. They advertise to capture our hands, which write the prescriptions, they capture our subconscious, and sometimes they capture free advertising space on our shirt, our coffee mug, our pen, our notepad, our stethoscope. The marketing strategies use proven methods of promotion. Otherwise they would not be using them. They are aimed at the subconscious, and they have effects which are unavoidable and unconscious. And the reason they use them is they work. It's that simple. And doctors don't want to accept this. It's really not a matter of choice.

Where do we fit in the picture as physicians? We are the ones who write the prescriptions. We are the ones who are driving the costs of pharmaceuticals. Healthcare costs are rising at a rate of about ten percent a year and the largest component of that is the cost of drugs. And we're the ones who write the prescriptions.

Now, what about conflict of interest? Conflict of interest is defined as a set of conditions in which judgment concerning a primary interest tends to be unduly influenced by a secondary influence -- or interest.

So many doctors would be willing to sign this, it is frightening. That stuff doesn't influence me at all. I just know -- I don't even know what drug is on my pen, I just go for the free food. So many people would be willing to admit that.

Former Surgeon General Everett Koop, he supported an extended patent for Claritin a few years ago. The Koop Foundation accepted a grant of a million dollars from Schering-Plough. What does Schering-Plough make? Claritin.

Okay. Koop was confronted with this information. He said I have never been bought. I cannot be bought. I am an icon. I have a reputation for honesty and integrity, and let the chips fall where they may. This is the surgeon general. I like Everett Koop. Don't get me wrong. I really like Everett Koop. One of his ex-secretaries was matron of honor at my wedding. But he's no different from anybody else. As far as being influenced by this stuff. He said it is true that there are people in my situation who could not receive a million dollar grant and stay objective, but I do.

Another quote. Power always thinks it has a great soul and vast views beyond comprehension of the weak. John Adams, letter to Thomas Jefferson. I think that's very appropriate to Dr. Koop's comment.

Conflicts of interest are institutional weeds. They take root below the surface, they become pervasive problems long before they show their ugliness. This is from the Widener Law Symposium Journal 2001.

I have other quotes. In the interest of time, I'm going to move on.

Are gifts a problem? Yes, they are. What do physicians think about receiving gifts? This is an internal medicine training program, 90 percent response rate. I won't bore you with the details. It comes down to this: Physicians were asked would you have a problem taking these gifts from a drug company? A \$40 textbook,

\$40 golf balls, free lunch with a rep, happy hour with a rep, without a rep, would you have a problem taking this? They surveyed both residents and faculty.

A textbook, no problem. Not even a mild problem. Not even a mild problem.

Golf balls. Well, some people had a mild problem taking golf balls with the drug company name printed on them.

What about free lunch? No problem.

Free lunch without a rep. Even less of a problem.

Happy hour with drug rep. Maybe a little problem.

Look at this. Look at this. Not one of them even got to be a moderate problem. So doctors are expecting this and they don't have any problem with it. Older data, not that old, two years old. But that's a little bit scary. That doctors are so willing to take this.

Great study. Principles and pens: Attitudes and practices of medical house staff toward pharmaceutical industry promotions, 2001 study, surveyed 117 young physicians in training, 90 percent response rate, attitudes towards nine types of promotion. This is the appropriateness of taking the drugs -- I'm sorry, of taking the gifts. This is just a survey.

How appropriate do you think it is to take a textbook, a lunch, a pen, a set of luggage from a drug rep? Very appropriate. Those are the numbers. Fifty-three percent said it was very appropriate to take an antibiotic guide. Only 80 percent said it was appropriate to take lunch. That's refreshing. Only one of out of 12 would take luggage with the drug rep on the side of it. Somewhat appropriate, and not appropriate.

Okay. This is a survey of attitudes. You know what they did next? They actually pulled all this stuff out for people. And guess what happened? All the people who said they would participate took this. These are the people who said that they would participate even if they considered it inappropriate. These are the people who said it is not appropriate to take a book or an antibiotic guide, and yet when that stuff was set on the table, they took it. So the attitudes and what they actually do are a little different.

This is probably my favorite slide. It's the other guy that I worry about. How much influence do drug companies have on my practice of medicine? Me and other guys. Okay? None, sixty-one percent. Absolutely no influence on the way that I practice medicine. Okay? A little bit, 38 percent. And a lot, one percent said drug companies affect the way I practice.

Now, what about the other guy? What about the person that I share an office with or the person I sign out my patients to or the person that I refer my patients to? What about him? Or her?

None, 16 percent; 51 percent a little; and 33 percent a lot. This is human nature. We are so willing to put these characteristics on others that we're not willing to assume ourselves.

Does that sound familiar? It is true that there are people in my situation who could not stay objective. But I do.

Pharmaceutical promotion. Get some good stuff here. 2004 pharmaceutical industry spent \$21 billion on promotion. That's a B, billion. Direct-to-consumer was 2.6 billion, physicians 18.4 billion. Where did this money go? Well, it kept going up, as you can see, from 1996. Why does it go up? Because it works.

For physicians, only \$480 million, half a billion dollars went into journal ads. That's only two percent. Detailing to hospitals, 4.1 percent. Detailing to doctors, notice this is part of promotion, dropping off free samples is promotion, and that's exactly where it's budgeted, 25 percent. Direct-to-consumer ads, 12.5 percent. And the rest is in samples. The rest is in samples. Fifty-six percent. Why the samples? We'll get into that.

Presently there are about 600,000 practicing physicians in the United States. You do the simple math and you see that the drug companies are spending an average of \$30,000 a year per physician to promote material to them. I don't know who's got my 30,000. Because I don't take any of it. So somebody got my 30,000. But this is

how strong the promotion is of the pharmaceutical industry. \$30,000 per physician per year. Imagine what could be done with that money. Imagine what good could be done with that money.

Direct-to-consumer ads. You know, we are one of two developed nations in the world that allows direct-to-consumer ads. The other one is New Zealand. There is no country in Europe that allows direct-to-consumer ads.

Look at how much this cost has gone up. This is the spending. Why has it gone up? Because it works. It was \$2.5 billion a few years ago. It's even higher now.

Radio and billboard, 11 percent. Print, you will notice that direct-to-consumer ads in print are more than direct-to-physician ads in print. Direct-to-physician ads were only a half a billion. To the consumers, it's 800 billion. Where is the rest of it? Television. \$1.43 billion spent on television ads for direct-to-consumer advertising.

What are Americans being sold? Article from Lancet in 2001. Sixty-seven ads were analyzed. Sixty-three percent of the drugs being sold were to ameliorate symptoms, 26 percent were to treat disease and 11 percent were to prevent illness. Mostly these are lifestyle drugs. Two-thirds of the ads make an emotional appeal rather than a logical or a scientific appeal. Two-thirds of the ads. Thirteen percent described the benefit of the medication using data. Only 13 percent, because the data's not that strong. Eighty-seven percent described the benefit using vague, qualitative terms rather than actual scientific data. Only half used data to describe side effects, and not one of these ads mentioned cost. Not a single one.

So how much of the drug company revenue is spent on each of these aspects? Twelve percent of revenue goes for research and development. Seventeen percent is profit that goes out to the shareholders. And 30 percent is in marketing and administration, and it's clever the way they do this, they combine marketing and administration together even though the vast majority of this turns out to be marketing.

Employees in 2000, this hasn't changed very much, distribution two percent, administration 11 percent, research and development only 22 percent, production and quality control, a little more, 26 percent. What's the rest? You bet. Thirty-nine percent in marketing. So that's where the money's going. It's going into marketing.

Pharmaceutical profits. For every industry in the United States, the median profit as a percent of revenue has been hovering somewhere between two percent and four percent, three percent and five percent. This is revenue, median profit as a percent of revenue. The drug companies are in a world by themselves and that is their profit as a percent of revenue. Up to 19 percent. So they are making big bucks, hand over fist.

U.S. drug expenditures have been going up year after year. You could just see it continuing to spiral upwards. Twenty-four percent is a shift toward expensive drugs, 37 percent is due to an increased cost of drugs, and 39 percent is simply due to writing more prescriptions. Americans are pill takers. This is a pill-taking society. We had a little conversation, a little discussion about this a couple of hours ago, trying to figure out exactly why, but it boils down to people want a quick fix. They don't want a doctor to sit and talk to them for ten minutes and the doctor doesn't want to waste the time, and be aware of the doctor who reaches for the pen when you mention a symptom.

Direct-to-consumer spending. Pepsi spent \$125 million in 2000. This is on direct-to-consumer spending. Budweiser spent \$146 million. And GM Saturn spent \$169 million. Okay. What's the missing bar in there? 2000. Vioxx. Vioxx spent more money than Pepsi and Budweiser in promoting the product in 2000, and what happened to Vioxx last year? Got pulled. Got pulled off the market. But that's how much money is out there.

Now, where, where do these drugs come from? Industry and research is really fascinating, and this is really kind of a topic all in itself. But I want to briefly go through this to try to help you understand. The industry designs and funds studies which are likely to favor its own products. They analyze their own data, they then hire ghostwriters to write the articles or to put their name on articles which are

written by professional medical writers, and if the data is not favorable, they suppress it being published. It doesn't get published with bad, bad news about particular drugs.

Here's a study. The Journal of General Internal Medicine looked at 107 controlled trials, they said did the author favor new drug versus old drug or did the author have industry support, and the trials funded by manufacturers of a new drug were significantly more likely to favor a new drug.

Cancer drugs. Studies that reached unfavorable conclusions about cancer drugs. Okay? If they were industry-sponsored studies, only five percent of those studies came up with negative results. If they were privately-funded studies, 38 percent showed negative results with cancer drugs.

Authors whose work supported safety of calcium channel blockers were more likely to be funded by drug manufacturers than authors whose work did not support the use of these drugs.

I gave a talk at MetroHealth earlier today, I talked a little bit about Norvast, which is a very expensive blood pressure drug which had been shown in a massive 42,000 patient study to be no better than hydrochlorothiazide which cost \$30 a year. This is an example of that.

We've got three major studies without industry support who have found a higher risk of blood clots for women who were using third-generation contraceptives. These are nonindustry-sponsored studies. The three studies that were sponsored by the drug industry did not show there was an increase in blood clots. Coincidence? Maybe.

Neurontin. 1994. Neurontin was approved by the FDA as a second-line seizure medicine, it was approved to be given as a drug in addition to what someone was already taking to prevent seizures. It was not a first-line drug. In fact, when they applied for first-line status, they were turned down. However, they did approve it for posttraumatic neuralgia, which is shingles, pain after shingles. Yet in 2003 Neurontin generated \$2.4 billion in U.S. sales. How in the world does a second line seizure drug generate \$2.4 billion and become the tenth biggest seller in the country, the tenth biggest profitmaker in the country?

Those are the other nine, by the way. You probably recognize the names of some of them.

Well, there was a supplement to a second line journal which came out and it had articles justifying the use of Neurontin in all of these conditions. Bipolar disease, pain syndromes, reflex sympathetic dystrophy, attention deficit disorder, migraine headache. This was all bad science. Not only that, all of these articles were ghostwritten, and they hired neurologists to put their name on them. They were all favorable to the drug company.

The government was not amused. In May of 2004 Pfizer was fined \$430 million for inappropriate promotion for off-label use of Neurontin. Nonetheless, speakers were paid big money to promote the off-label uses, as I said before, the articles were ghostwritten, and the fact is, when you got \$2.4 billion in sales, a \$430 million fine is just the cost of doing business. Because doctors have not stopped writing for these unindicated uses, I assure you. I still see patients coming in who are taking Neurontin for things that it's never been approved for.

Okay. They blinded me with science. How do they do this? Drug companies do not test their drugs in sick patients. Unless they have got a particular drug that they want to show works in a particular population. They test their drugs in a healthy population rather than the patients who may actually end up receiving it. This makes the drugs appear to have fewer side effects.

And a perfect example of this is the nonsteroidal antiinflammatories. In the original studies for nonsteroidals, one in 50 patients was over the age of 65. Yet this is the primary group that doctors are writing for, the over 65 patients. And once the older patients started taking them, the side effects showed up, the adverse effects, the GI bleeding, the other problems.

Trials are designed in certain ways to make the end results look good. They use surrogate endpoints. In other words, they may use an endpoint for a breathing medicine of an FEV-1, which is a measure of pulmonary function. That's a surrogate endpoint. A more useful endpoint might be how many times did this patient have to be hospitalized? That's something that is usable. Other usable endpoints are things like death, stroke, heart attack. But so often you will see these studies using surrogate endpoints.

In the cardiovascular work you are going to see a lot of reference to what is called TIMI III flow. Based on a study done years ago, the TIMI III trial talks about blood flow through coronary arteries. That's a surrogate marker. Nobody talks about increasing -- or decreasing mortality because that data didn't work. It didn't decrease mortality. It just improved the flow in the coronaries.

Important endpoints, as I mentioned before, death, disability, prolonged hospital stay, adverse effects.

They will do strawman comparisons. This is one of the favorites. They will take a good dose of their drug and compare it to a low dose of another drug and say, well, our drug is obviously better. They do this all the time. You have to be cautious and look at the doses of the drugs they are using in the study.

Here's a study that looked at all the NSAID studies and discovered, guess what, whoever sponsored the study always got a better result than the comparator. In 48 percent of trials, the reason for that was because the dose of the sponsored drug was appropriate and the dose of the drug that it was being compared to was less than appropriate. The strawman study.

You can get the results you want by doing a lot of things, if you are a drug company. You can do a trial against placebo. To get a drug approved by the Food and Drug Administration, you don't have to prove it's better than anything else. You have to prove it's better than nothing. You do not have to prove that it's better than anything else that's on the market. So a lot of these studies are done with placebo trials. Or they will do a trial against an inferior treatment, a trial against a low dose, like I mentioned before. Or they will do a trial against a high dose if they are trying to prove there's less toxicity with their drug. They will have what's called an equivalence trial which is too small to show the difference from the competitor drug.

One of my favorites was the composite endpoints. They will say, well, we looked at this drug and we decided the endpoint was death or stroke or heart attack or toenail fungus. And we decided that this drug reduced the end component. Okay? Well, if you look at the individual data, you may find out it didn't make a bit of difference in death or stroke or heart attack, but it did a whale of a job taking care of toenail fungus. So that's how they got that result, by using the composite endpoints. It's the principle that if you set up four targets at the other end of the room and you are not a very good shot, you are more than likely to hit one of those targets.

Subgroup analysis. Always dangerous. There was a subgroup analysis of a major cardiology trial a few years ago, huge trial, 40,000 people, and by looking at the subgroup analysis, they proved that if you were a Libra or a Gemini, aspirin didn't work if you were having a heart attack. I'm serious. That's the danger of doing subgroup analysis. You can make numbers dance and sing. This is why subgroup analysis is also called data dredging. That's another name for it. Data snooping. Because we have got such fantastic computers and software nowadays that we can plug in all these numbers and we can make something look significant. That's not science. Science is determining what you are going to do at the beginning and sticking with it. It's not going back and dredging through the data and seeing what looks significant.

And then the other thing they do, how many times do physicians actually get to read negative studies? There are file cabinets across this country full of negative studies that never got published. Because nobody wants to publish a negative study. Where's the glory in that? Where's the glory in saying I spent four years of my life and proved that two things were exactly the same? So that type of stuff doesn't get published.

Something else they do is they will publish the same study, a positive study, in several different journals or in supplements, they will publish different outcome measures at different times.

This is one of the complaints with Celebrex. The initial article in the New England Journal on Celebrex said that at three months there was less GI bleeding. What they didn't tell you was that they had data out to six months and at six months there was absolutely no difference in GI bleeding. Until the Washington -- I think one of the Washington newspapers actually dredged that data up.

These are just some other examples of the way you can take data and make it dance and sing and make it do the things you want. You have to be very cautious. Physicians have to be very, very careful about this material.

All I know is what I read in the journals. Right? Well, quote from the New York Review of Books. Journals have devolved into information laundering operations for the pharmaceutical industry. That's a shame. That's a shame.

In 1987, the manufacturer of levothyroxine, Synthroid, contracted with a University of California researcher, they paid her to compare their product with the generic forms of thyroid that were on the market. She did the data, she did the work, it was a beautiful study, it was an elegant study, and she proved there was absolutely no difference between Synthroid and all of those generic thyroids that were on the market.

The company not only refused to allow the findings to be published, they sued her when she tried to publish them independently. And this was the subject of a huge brouhaha several years ago. It ended up as a separate article in the New England Journal called Thyroid Store. Which is a good pun, actually.

The Immune Response Corporation contracted with UCSF performed randomized controlled trials for the immune modulator to treat AIDS. It showed no effect, and when the researchers tried to publish these results, they were again stopped by the company. They said you cannot publish that data. We did not approve it. Even though they hired them to do true scientific work.

1996, deferiprone, used to treat thalassemia major, could worsen hepatic fibrosis, in other words, some liver problems. And the trial sponsor threatened, again, legal action, we will sue you if you publish this information, which we hired you to research, by the way. So there's example after example of this.

This is one of my favorites. 106 reviews of passive smoking, of which 63 percent said it was harmful and 37 percent said it was harmless. Well, they did a multiple regression analysis, they looked at the quality and the peer review and the year of publication and everything else, the only factor which fell out was whether the author was affiliated with the tobacco industry or not. That was the only thing that made a difference.

Survey, 192 authors of 44 clinical practice guidelines, 87 percent of the authors, this is clinical practice guidelines, this is what we're supposed to treat patients based on, the best evidence available, 87 percent of the authors had some form of interaction with the pharmaceutical industry. And yet in the published versions of these guidelines, specific statements about personal financial interactions were made in two cases.

There are better examples of this. The American Heart Association, this was a big, big problem, Class I, which means definitely recommended, tPA for stroke, despite controversy about its safety, about its efficacy that is still raging in the emergency medicine and the neurology community, yet the American Heart Association made it a Class I recommendation with its last update.

Most of the American Heart Association stroke experts have undisclosed ties to Genentech, the manufacturers of tPA, and Genentech contributed more than \$11 million to the American Heart Association in the ten years before the AHA recommendation. If you go to the American Heart Association headquarters on Greenville Avenue in Dallas for a meeting, you will go to the Genentech Meeting Center, which is named for the drug company which contributed the money. And that is a shame.

Now, when the original recommendations came out, they said tPA saves lives. The data does not show that. And enough people protested that they got the American Heart Association to pull that. It does not save lives. Thus, even a seemingly impartial nonprofit organization that issues professional guidelines that we have to follow and that lawyers look at to determine whether somebody has committed malpractice, these guidelines can be bought.

The flak man cometh. Now we're going to talk about detail a minute.

How we doing on time?

Okay. Physicians have been characterized into four different types. There are the sheep who are primarily interested in maintaining conformity. There are the wolves, who are primarily interested in making money. And we have got these in our profession just like you've got those in your profession. There are the bunnies, and I'm a bunny, we like taking care of sick people. That's what we do. And then there are the dodos, and the dodos are the burned out, and their primary concern is survival.

Now, the reason that this is important is because in the pharmaceutical promotional magazine *Scrip* you will see a takeoff on the musicians of Bremen with the wolf and the sheep and the bunny and the dodo, and this particular issue tells the pharmaceutical representatives how to approach each of these categories of physicians. Because the approach will be different for each one of them.

Promotional honesty. What about the materials that a drug rep actually hands out? What's the appropriateness and what's the value of it? This is a study where they looked at all materials left behind by drug reps or mail over a seven-month period. 482 pieces of promotional material. They looked at it scientifically, they said does it meet the FDA requirements for balance, adequate instructions for use, and discussion of approved uses only, and lo and behold, they discovered that about a third of it lacked fair balance, nine percent lacked instructions, and even four percent, one in 25, talked about unapproved uses, which is very much verboten. The FDA does not like it if you promote drugs for off-label use. Forty-two percent of this material failed to comply with at least one FDA criterion for promotional material from drug companies to doctors.

What about the accuracy of information from pharmaceutical sales representatives? Article in *JAMA* about ten years ago, this is a house staff conference, it's standard in every academic program in the country, there was a pharmacist in the front row with a tape recorder and he recorded all of the comments made by drug reps prior to the faculty lecture. Some places still do this. Before the lunch conference, the lunch is purchased by a drug company, and they allow this drug rep to stand in front of a group, like this, and show their product. This pharmacist sat in the front row, he recorded this, and then he analyzed 106 statements made by drug reps at 13 different conferences and classified what they said as either accurate or inaccurate.

Every inaccurate statement that was made was favorable to the drug. Every inaccurate statement was favorable to the drug. There were 11 percent of the statements that were made that were just flat out inaccurate. And the scary thing is the residents at these conferences remembered 26 percent of those inaccurate statements as being accurate.

How about the journal inaccuracy? Pharmaceutical advertisements in leading medical journals. This was actually kind of clever. 109 ads which were submitted in peer reviewed journals. They took the peer reviewers and they said if this ad were submitted as an article, would you publish it? This is just going through some of the criteria. I don't expect you to read these. Thirty percent, 30 percent of these submitted ads disagreed -- I'm sorry, the data disagreed with the ad claim. I'm a little ahead of myself on this. Thirty percent disagreed with the ad claim, 44 percent would lead to improper prescribing, 57 percent of these ads had absolutely no educational value, and 92 percent, the ad was not in compliance with one or more of those FDA criteria that I just ran by you.

This is, this is the one I was thinking of. I was one ahead of myself. Would you accept this ad in its present form, would you accept this ad with minor revisions, with major revisions, or would you reject this advertisement? This was presented to peer reviewers, the ads. Eight percent said they would accept the ad as is, 34 percent accept with minor revisions, 34 percent with major revisions, and 24 percent would reject the ad based simply on the science. Because it wasn't scientifically valid.

Let me move through, I want to mention this one, my favorite phrases in pharmaceutical promotion.

Unsurpassed efficacy. Now, that sounds good. Unsurpassed efficacy. Wow. Think about what that means. Unsurpassed means just as good as. And yet you will hear drug reps talk about unsurpassed efficacy of their drugs all the time, now. All that means is it's just as good as what else is out there on the market. It doesn't mean it's any better. It's just fancy words to say the same as.

Zyprexa. Zyprexa was approved for treatment of schizophrenia and maintenance treatment of schizophrenia, treatment of acute mania associated with bipolar disease, and maintenance treatment of bipolar disorder. Those are the only four indications for Zyprexa. And yet in 2002 this was the single largest medication expense for Medicaid programs in Kentucky, Indiana and Tennessee.

Now, what do those three states have in common? Kentucky, Indiana, Tennessee. They're all lumped together. Who makes Zyprexa? Eli Lilly. Where's Eli Lilly's home? Indianapolis, Indiana. Probably just a coincidence, right?

The Kentucky legislature considered excluding Zyprexa from payment because the indications weren't there. Two nonprofit citizen groups sprang into action, they had rallies at the state capital, they had fax campaigns, they had full ads, full page ads in the newspapers, and guess what? Eli Lilly paid for the buses, they paid for the faxes, they paid for the newspaper ads.

Zyprexa in 2003 sold \$3.2 billion as an antipsychotic for schizophrenia and bipolar disease. Those are the only indications for that drug. And yet it sold \$3.2 billion.

So where's the government in all of this? Well, let's see. Former President George Bush is a member of the Eli Lilly board of directors, Ken Lay is a member of the Eli Lilly board of directors, director of management and budget Mitch Daniels was Eli Lilly's vice president, and Homeland Security Advisory Council member Sidney Taurel is the CEO of Eli Lilly. So where is the government in all of this?

And then there's Provigil. Provigil was approved by the FDA for narcolepsy. And then in 2003 the Primary Care Companion in the Journal of Clinical Psychiatry dedicated to medical conditions characterized by fatigue, depression, executive dysfunction, shift work sleep disorder, which all ER docs suffer from, shift work sleep disorder, because we are shift workers, and this was a supplement which was published in the journal that paid the lead authors of all eight articles in the supplement, and Provigil is now being promoted to ER docs as a treatment for shift work sleep disorder. It's actually been approved for that indication now. It's not been approved for the other indication.

There's lots of other examples. COX-2s, I'll briefly mention them, but the point is The Washington Post is the organization that the FDA had the full results of the CLASS study about Celebrex causing just as much GI bleeding in six months, and it was never, never promoted. It was never -- Pfizer continues to use earlier reprints of the bad study, which has now been rejected, and many family docs don't realize that there's newer data out there that show Celebrex is no better than the cheaper stuff. Celebrex is two bucks a tablet, ibuprofen is about a nickel a tablet, and they are about the same as far as side effects.

Then there was the VIGOR study in the New England Journal in 2000 which showed that Vioxx seemed to show cardiovascular toxicity. 2000. What the company claimed was that the comparator was cardioprotective, not that Vioxx was poisonous. And yet the comparator had never been shown to be cardioprotective. And, of course, a few years later they just pulled it off the market. Long-term trial confirmed cardiovascular toxicity. So this stuff is still going on.

Reprints are a big problem. Drug companies may buy as much as a million dollars' worth of reprints from journals. Now, journals have to sell ad space so they can put their material out. Physicians, I hate to tell it to you, but physicians are cheap. Physicians don't want to pay 150 bucks a year for a subscription for something. They will pay less than that, but to get it for less than that, that means that the journals have to sell space to the drug companies.

So these are a major source of revenue for the journals which publish the trials. These are handed out to doctors all the time. The doctors never read them. But they are handed out, and somehow this journal article branded, it sells, it adds luster to the selling points. There's a major conflict of interest for journals. Because sometimes what they have is publish this paper and get a million dollars for reprints or lay off six editors. Major conflict of interest.

It's a major source of revenue, especially for the second tier journals, and it often includes papers presented at drug-sponsored symposia, the editors are often the people running the symposia, it's just all mixed together. And then the studies are only selectively published. So it's a real mess. You've got to pay attention to stuff like this.

I'm going to go -- we're running out of time. I want to show you this. This is a logical fallacy. There are many logical fallacy in pharmaceutical promotion. I want to show you the fallacy of celebrity. I love this.

Once-a-day Prinivil for blood pressure. Just like Cal Ripken. Both on the job every day. What's that little bitty print down there that says Cal Ripken, Jr. is not hypertensive and is not taking Prinivil. It's there, but you've got to look for it. But you have heard the ads.

Mickey Mantle was promoting Voltaren before he died. Lauren Bacall is out there promoting drugs. It's the fallacy of celebrity. You know, if Brad Pitt takes this drug, then I should be taking it also and I'll be more like Brad Pitt. Now, it may be a bad example, I don't know.

What do our patients think? Well, I know what the cartoonists think. You can find cartoons like this all over the place. And this certainly makes our profession look bad.

These used to be posted around hospitals. What do my patients think when they see that I can go to the AstraZeneca and pick up my Easter ham just by listening to a drug rep give me a little spiel? Or the Floral & Dash. Unfortunately this is another AstraZeneca. I'm not picking on them. Those are just two examples that I have.

Now, I am not a friend of big pharma. But you know something, I still get stuff like this. This is from earlier this year. They are going to invite me to the Ritz-Carlton Hotel in Washington, D.C., and pay me \$1,500 to sit there and listen to some drug rep talk to me and try to convince me to push their drug. I took out some of the identifiers there, but I just wanted to show you that this stuff still goes on, even for somebody like me who has been talking against this stuff for years.

Patient perceptions. Let's just say that the patients recognize what's going on and they don't like it. They don't like it.

Now, let me go through and get to some other ones, because, as I said, this is a huge amount of material.

This is a great quote and, from all places, USA Today. Such gifts would trigger a big red bribery alert in the mind of just about any public official or government contractor, but not in the minds of many doctors, raking in jaw-dropping gifts from pharmaceutical firms.

We just sort of accept it as a matter of course. And I think we need to change this.

And if you are curious about more information, there are so many books out there, it will make your head spin. These two are probably my favorites, the Marcia Angell and the Jerry Avorn. The Truth About Drug Companies, Powerful Medicines. If you go to Amazon.com and you put one of these in, it will tell you people who bought this book also bought these others. On the Take: How Medicine's Complicity With Big Business Can Endanger Your Health.

Jerry Kassirer was an editor for the New England Journal. Marcia Angell was an editor of the New England Journal. These are not smalltime people trying to make a name for themselves. These are people who were in the business who saw what was happening and then decided to expose it when they got out.

Overdosed America, John Abramson. It goes on and on. The \$800 Million Pill, The Big Fix. There are plenty of books out there, all published in the last couple of years.

It is 6 o'clock. I am going to stop here. I've got a bunch more. This is actually as many as, I think I've got 292 slides, and there's absolutely no way I can get through those even in two hours, but I hope that I was able to get my point across to you. This is a big problem for medicine that we're trying to deal with, I hope a little at a time. There are a few of us out there who are preaching the message to other doctors and trying to get them to understand how pervasive this is and how important it is.

I hope it was helpful for you to understand a little bit, as a lawyer, to understand what influences doctors are coming under here, but also to see what the drug companies are doing. And again, to emphasize the point, that I don't consider drug companies to be evil empires. I consider them to be businesses who are following their own ethics, which are different from our ethics. And we have to keep in mind our patients or our clients and not profits, which is what they are involved in doing. So yes, sir.

PARTICIPANT: Okay. I enjoyed your lecture, first of all [inaudible].

Secondly, I think at the beginning you said about how drug companies give away freebies based on drug samples to physicians.

DR. LEX: Yes. Okay.

PARTICIPANT: Now, what is the harm in that? Because they can't sell it to the patients.

DR. LEX: No, what happens is -- if you are willing to stay. I understand people have to leave, but the harm is -- where is it? Okay. The effect of drug sample availability on physician behavior. They looked at a series of doctors and gave them hypothetical scenarios, uncomplicated urinary tract infection, high blood pressure, and depression. They then surveyed the doctors and said what would you use to treat these conditions? I would use a diuretic or a beta blocker as initial therapy. Ninety percent of the doctors said that. Okay? This is correct. This is what the ALLHAT study showed. Hydrochlorothiazide, a diuretic, is the appropriate drug to start somebody on.

Then when they made samples of more expensive drugs available by freebies, 32 out of those 35 doctors gave a more expensive sample than the inexpensive drug they would have started somebody on. Okay. Well, what's the point to be made there? Hypertension followup, patient now has health insurance, the blood pressure has been controlled on the sample drug. The blood pressure probably would have been controlled on the cheap drug also. But now that it's controlled on the sample drug, a prescription is written for that sample medication 69 percent of the time. They did not switch back to the sample or back to the hydrochlorothiazide.

Sample users wrote for a drug different from the one that they predicted they would use 88 percent of the time when those samples were available. And that is why drug companies do it. They do it because they know physician behaviors, they know that physicians will continue to write for that drug when the patient is able to pay for something more.

I've got more material on that. I want to show you something else, when you say what's the harm in the samples. This is one of my favorites.

Personal use of drug samples by physicians and office staff. So you have got all these free samples sitting in the office. How many of those actually get handed out to patients? Well, a lot of people help themselves. Twelve faculty, 21 residents, eight nurses, nine office staff, and three unknown took drug samples. Okay? 230 samples were taken. 152 were for personal use and 78 percent were to give to a family member. Hmm. Okay. Cost of the samples was about \$10,000.

Now, this is even better. This is pharmaceutical reps with their samples. Do they use their own samples? Not only do they use their own samples, 59 percent of them provided samples to other than physicians, so they are prescribing drugs without a license, and 48 percent either self-medicated or provided samples to friends or relatives. So half of the drug reps are handing out their drugs to nonphysicians. Twenty-six percent were swapping with other drug reps. Ooh, yeah, you have got some Avelox. I'll trade you some Celebrex for your Avelox. And they were swapping these drugs back and forth.

So this is the problem with samples. Samples lead to bad prescribing. They do not do our patients any favors.

I work in an emergency department. I have a very financially vulnerable population of patients. And I try to write for the cheapest possible drug I can write for on a day-to-day basis, because there's no benefit in me giving somebody a drug which is going to cost \$120 a month if they have to continue on that drug, and if I give them a sample for one of these drugs and they go to their family doc and their family doc finds out that drug is working, the inclination is to keep prescribing that same drug. And that patient cannot afford that drug.

So that's why samples are bad. That's why samples are bad.

Okay. Other questions? Okay. Thank you. Yes, sir.

PARTICIPANT: I was just going to say are pharmacy benefit managers countering the efforts of branded drugs by pushing generic? It seems --

DR. LEX: Oh, absolutely. Yeah, pharmaceutical benefit managers, yeah. We're asking the wrong questions in this country. The government is asking the wrong questions. Instead of saying how are we going to pay for drug benefits for the elderly, we should be asking the question which drugs are useful in the elderly? Because I think three-quarters of them are useless or possibly even harmful. And I think pharmaceutical benefit managers may be the people to ask those questions. They should not be saying how could I cut costs, they should be saying which of these drugs is actually going to help the people who are in my plan? And I think that should be the government's job also, but the government is not prepared to take that up. Instead they are trying to find ways to finance giving bad drugs to people. Or giving useless drugs or giving expensive drugs to people. But I don't think those are the answers. I really don't.

Yes, sir.

PARTICIPANT: She just turned around.

DR. LEX: Oh, yes. Hi.

PARTICIPANT: Yeah, I was very interested in the outcome of the lawsuits to suppress the scientists who have done studies that were not favorable. Were they able to do it?

DR. LEX: They were not. Because the publicity got out and the general uproar from the medical community was such that the companies dropped the suits.

PARTICIPANT: Yeah, but in other words, the authors were still harassed by the pharmaceutical companies?

DR. LEX: Oh, absolutely. Absolutely. Especially Dr. Dong, the physician who did the thyroid, she was actually fired from the University of California and had to sue to get her job back. Because of all of the grief that was brought down on the University of California. And that was a real mess.

PARTICIPANT: I believe that.

DR. LEX: It's very instructive to go read that article in New England Journal called Thyroid Storm. It walks through the entire process of what happened.

Okay. Yes, sir.

PARTICIPANT: You mentioned the use of subgroups for getting drugs approved. I remember a month or two ago there was a big hubbub over a drug that was coming out and it hadn't been approved because the data wasn't there, then they went back and looked at it and they thought that they were getting it approved for use in the African American community.

DR. LEX: Yes, BiDil. BiDil. That's a perfect example of subgroup analysis. That's exactly what happened. They had this combination drug, a diuretic and an ACE inhibitor, and when they did the initial studies, it didn't seem to offer any benefit over anything else except when they did a subgroup analysis and saw that in the African American community it seemed to be more cardioprotective.

The interesting thing is there's another drug, the statins, the statins actually seemed to work better in preventing cardiac disease in asymptomatic African Americans, but nobody is going out of their way to promote that right now. The statins are such big sellers anyway. I mean everybody, gee, people are taking Lipitor and all these other drugs like crazy. The data's kind of weak. Unless you have already had a cardiovascular event. In fact, there's pretty good data that unless you have a cardiovascular event, they don't do anything. Except in African Americans. And there it does seem to decrease the amount of cardiovascular disease.

Yeah, they made it sound like it was racially tailored, but it wasn't. It was, I think it was more of a result of subgroup analysis.

DR. LEX: Thank you.